BIOWORLD™ TODAY

THE DAILY BIOPHARMACEUTICAL NEWS SOURCE

OCTOBER 1, 2014 BIOTECH'S MOST RESPECTED NEWS SOURCE FOR MORE THAN 20 YEARS VOLUME 25, NO. 190

STEALTH WEAPON IN NUKE WAR?

Under an 'Alios': J&J's $1.75B takeover means RSV upside but HCV candidate motivates, too

By Randy Osborne, Staff Writer

Would-be therapies in respiratory syncytial virus (RSV) took center stage with Johnson & Johnson's (J&J) plan to take over Alios Biopharma Inc. for $1.75 billion, gaining a pipeline that includes the phase II oral nucleoside analogue AL-8176 in RSV and a uridine nucleotide (nuke) analogue, AL-335, for hepatitis C virus (HCV) – another, less loudly touted driver for the deal.

Alios' press release seemed to highlight the RSV aspect, but analyst Michael Yee with RBC Capital Markets called the buyout "a hep C nuke acquisition in disguise," noting

See Alios, page 3

THINKING 'BROADLY AND STRATEGICALLY'

Takeda 'DARTs' back for seconds in potential $1.6B Macrogenics deal

By Marie Powers, Staff Writer

Four months ago, Takeda Pharmaceutical Co. Ltd. took an option to develop and commercialize MGD010, a preclinical asset developed in-house by Macrogenics Inc. that uses its Dual-Affinity Re-Targeting (DART) technology to simultaneously engage the B-cell surface

See Macrogenics, page 4

DEALS AND M&A

Pfizer, Kyowa Hakko combining antibodies in immunotherapy deal

By Cornelia Zou, Staff Writer

HONG KONG – An American pharmaceutical firm is working with a Japanese biotech company to combine two antibodies into a more effective immunotherapy for solid tumors.

See Pfizer, page 5

THE BIOWORLD BIOME

Chinese researchers find promising new target for obesity drugs

By John Fox, Staff Writer

HONG KONG - For the first time, Chinese scientists have identified the molecular mechanism underlying the anorexogenic effects of a safe and effective herbal dietary supplement that is widely

See Obesity, page 6

NEWCO NEWS

FINANCINGS, LICENSING, PURCHASE

Round two for former Pharmasset execs with HBV start-up Oncore

By Marie Powers, Staff Writer

After operating off the grid for nearly two years, Oncore Biopharma Inc. has unveiled three recent deals to mark its presence in the hepatitis B virus (HBV)

See Oncore, page 7

CORTELLIS

For a deeper dive: BioWorld is now linked to Cortellis

Breaking news often is the start of something bigger for drug developers and companies in the surrounding orbit. Starting with today's edition, BioWorld will include direct links to Thomson Reuters Cortellis for companies and

See Cortellis, page 8

REGULATORY

Sunshine payments database stokes fear among docs, industry

By Michael Fitzhugh, Staff Writer

The Centers for Medicare & Medicaid Services (CMS) Tuesday launched its official Open Payments website, an online database consolidating public information on payments made by drug-

See Sunshine, page 9

IN THE CLINIC

4SC, Yakult Honsha take HCC therapy forward into phase II

By Kristine Yang, Staff Writer

HONG KONG – A German-Japanese effort to develop a first-line therapy for advanced Asian hepatocellular carcinoma (HCC) recently hit an important milestone with the completion

See Yakult, page 10

FINANCINGS

Alimera Sciences Inc., of Atlanta, said it received a $25 million advance from Hercules Technology Growth Capital Inc., the second and final advance under the loan and security agreement inked in April between Hercules and Alimera's UK subsidiary, Alimera Sciences Ltd. Receipt of the final advance was conditional on the approval, on or before Oct. 31, 2014, of intravitreal inplant Iluvien by the FDA. Iluvien gained approval Sept. 26 for use in patients with diabetic macular edema. Alimera wil use the $25 million to fund a $25 million milestone payment owed to the licensor of certain intellectual property as a result of the recent FDA approval. (See *BioWorld Today*, Sept. 30, 2014.)

Allakos Inc., of San Carlos, Calif., secured an additional $10 million investment to fund development of an additional undisclosed therapeutic antibody, which the company advanced into preclinical studies. The financing, which extended the company's series A round to $42 million, was completed after Allakos achieved a pre-specified milestone related to its lead antibody program targeting multiple allergic and inflammatory diseases. All of the company's current investors, which include Novo Ventures, Alta Partners, Rivervest Venture Partners and the Roche Venture Fund, participated in the financing.

Argos Therapeutics Inc., of Durham, N.C., said it entered a $25 million venture loan led by Horizon Technology Finance Corp. to continue the development of AGS-003, its lead oncology candidate, which is being evaluated in the pivotal ADAPT phase III trial in metastatic renal cell carcinoma, and to expand development of its Arcelis technology platform, including the leasing, build-out and equipping of its planned automated commercial manufacturing facility. The loan is available in two tranches of $12.5 million. On Sept. 29, the company closed on the initial tranche, which is a four-year senior secured term loan that bears interest at a floating coupon rate of one-month LIBOR plus 8.75 percent and includes an initial interest-only period of two years. The second tranche, which includes an initial interest-only period of 18 months on a 42-month senior secured term loan at the same terms, is conditioned on completing the enrollment and randomization of patients in the ongoing phase III trial of ASG-003. In February, Argos closed its initial public offering, raising $45 million to support the study, which is expected to report data in the first half of 2016. (See *BioWorld Today*, Feb. 10, 2014.)

Coming Thursday in *BioWorld Highlights*:

EMERGING BIOSIMILAR MARKET KNOWS NO PARALLEL

It's not every day that drugmakers get a chance to take on an entirely new market. Biosimilars are offering that opportunity. And hundreds of drugmakers, research institutions and governments are hoping to make the most of it. The result is more than 700 follow-on biologics (FOBs) already approved or in the global pipeline, according to a new report by BioWorld. To read more, see tomorrow's edition of *BioWorld Highlights*, a free weekly ezine that provides articles from *BioWorld Today*, *BioWorld Insight* and *BioWorld Asia*, plus insight and opinion from the *BioWorld Perspectives* blog, http://bioworld.blogs.bioworld.com. If you don't already receive this complimentary e-zine, click here to opt in.

STOCK MOVERS 9/30/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	-$29.58	-1.02%
Agios Pharmaceuticals Inc.	-$5.15	-7.74%
Catalyst Pharmaceutical	+$0.33	+11.04%
Endocyte Inc.	-$0.91	-13.02%
Esperion Therapeutics Inc.	+$2.10	+9.39%

Biotechs showing significant stock changes Tuesday

BIOWORLD TODAY

BioWorld™ Today (ISSN# 1541-0595) is published every business day by Thomson Reuters, 115 Perimeter Center Place, Suite 1100, Atlanta, GA 30346 U.S.A.

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Alios

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that Alios not only has AL-335 with potent preclinical activity across HCV genotypes, but also AL-516, a purine nucleotide analogue in preclinical studies going into phase I next year.

The boards of South San Francisco-based Alios and J&J, of New Brunswick, N.J., have agreed to the deal, expected to close in the fourth quarter of this year. Alios could not be reached, as the companies were holding an all-hands meeting Tuesday to explain what the takeover will mean for employees.

"We generally agree that the deal was in good part for RSV drug AL-8176, which has completed positive phase II data similar to Gilead Sciences Inc.'s positive phase II data earlier this year," Yee wrote in a research report, but the HCV piece is important. Alios also has candidates for influenza and rhinoviruses.

In RSV, Foster City, Calif.-based Gilead is working on the oral fusion inhibitor GS-5806; J&J may have an internal program with a fusion inhibitor, too. Wells Fargo analyst Brian Abrahams said "the price paid [in the Alios deal] highlights the significant opportunity and unmet need in RSV, where there are 150,000 hospitalizations per year for children alone, with upwards of 178,000 hospitalizations per year among elderly patients." Gilead's compound is underappreciated, Abrahams wrote in a research report, conceding that AL-8176 is undergoing tests in hospitalized infants but GS-5806 has yet to move into pediatric trials.

In HCV, AL-335 differs structurally from Alios' nuke analogue, VX-135, which targets the NS5B polymerase and is partnered with Cambridge, Mass.-based Vertex Pharmaceuticals Inc. VX-135 was the subject of a potential $1.5 billion deal with Alios in 2011, but it ran into problems when patients developed elevated liver enzymes. Earlier this year, Vertex said no further investments would be made in the asset and the firm would try to out-license it. AL-335, for its part, yielded promising preclinical data at the American Association for the Study of Liver Diseases meeting earlier this month. (See *BioWorld Today*, June 14, 2011.)

Others in the HCV space include Achillion Pharmaceuticals Inc., of New Haven, Conn., suggested by some as a potential takeover target for J&J or another big pharma concern. Achillion is developing ACH-3422, a nuke pro-drug of a uridine analogue for HCV. In June, the company began dosing for seven days in patients with genotype 1 chronic HCV as part of the ongoing phase I trial, with proof-of-concept results due this fall, which puts the candidate well ahead in the race and thus "attractive to J&J or others hoping to compete in the HCV space," in Abrahams' view.

HERE COMES LVD/SOF, TOO

Alios' RSV therapy has turned up positive data after treating healthy volunteers infected with RSV within 12 hours, similar to Gilead's program, "so we will continue to watch this, which in some ways 'validates' Gilead's RSV program and opportunity," in the opinion of Yee, who estimated that an RSV drug could be a $1 billion product.

At the same time, "we clearly think the long-term 'call option' upside here is the Alios nukes, if those can show a 4-log reduction in HCV virus and have a good safety profile," Yee wrote, acknowledging such an outcome "is not a lay-up, as we know development of nukes can be extremely difficult and the bar for continued progression is very high." Vertex, for example, he reminded investors, dropped not only VX-135 but another nuke, because of low efficacy.

In June, big pharma's appetite for HCV nukes was proved by Whitehouse Station, N.J.-based Merck's buyout of Idenix Pharmaceuticals Inc., of Cambridge, Mass., for $24.50 in cash per share, or about $3.85 billion, in a 300 percent-plus premium. Merck reaped Idenix's IDX21437, a uridine nuke analogue NS5B polymerase inhibitor for which the firm had just disclosed data from a phase I/II trial. During the seven-day proof-of-concept part of the study, IDX21437 yielded mean maximum 4.2 log10 IU/mL to 4.3 log10 IU/mL reductions for patients infected with HCV genotypes 1, 2 or 3 receiving 300 mg once daily. Results with IDX21437 stacked up against Gilead's Sovaldi (sofosbuvir) in the same class. Multiple bidders came to the table for Idenix, making Achillion's program likely soon to find a buyer. Approved late last year by the FDA, Sovaldi has established efficacy as part of an HCV regimen in patients with genotypes 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma who meet Milan criteria (i.e., awaiting liver transplantation) and those with HCV/HIV-1 co-infection. (See *BioWorld Today*, April 24, 2014, and June 10, 2014.)

Deutsche Bank analyst Alethia Young noted that J&J recently reported $900 million in quarterly sales with its HCV protease inhibitor Olysio (simeprevir) combined with Sovaldi. "This combo is off-label and likely will get limited use after Gilead's all-oral [regimen] is approved in early October," she wrote in a research report. Gilead in April said the FDA granted priority review to the company's new drug application for a once-daily fixed-dose combination of the NS5A inhibitor ledipasvir 90 mg and Sovaldi 400 mg, often called LVD/SOF, in adults with chronic HCV genotype 1 infection. The PDUFA date is Oct. 10.

"Alios plans to start its phase I program around year-end with [its] nuke, so at fastest would give Achillion around a nine-month lead," Young pointed out in a research report. "We think developers will look for phase II-ready assets in the next 12 months," as was the case with Idenix. "We still view Achillion's data readout in phase I as a highly relevant catalyst and [could provide] a meaningful lead over competitors," she added. //

Macrogenics

Continued from page 1

proteins CD32B and CD79B, targeting autoimmune diseases. The Osaka, Japan-based pharma apparently liked what it saw, using that deal to segue into a collaboration to develop and commercialize up to four additional candidates.

Under the new arrangement, Takeda took an option to an exclusive worldwide license to each of four product candidates and will fund all research and development activities related to the programs, including reimbursement of Macrogenics' expenses. Assuming successful development and commercialization by Takeda, Macrogenics stands to receive approximately $400 million in additional payments for each candidate, or up to $1.6 billion, based on program initiation, preclinical, clinical, regulatory and commercialization milestones. Macrogenics also is in line to receive double-digit royalties on global net sales, and it retained the option to co-promote each candidate with Takeda in the U.S.

Rockville, Md.-based Macrogenics also may elect to fund a portion of phase III development for any or all of the four candidates in exchange for a North American profit-share.

The therapeutic targets were characterized only as "critical diseases" in the autoimmune space. Each product candidate will be directed against jointly selected pairs of molecular targets and will incorporate the DART platform.

Unlike their first arrangement, the new terms put Takeda in the driver's seat early on. In the deal inked in May, Macrogenics received $15 million up front to conduct development activities through a pre-defined phase Ia study. At that point, Takeda may opt for an exclusive global license and assume responsibility for further development in exchange for a combined $18 million early development milestone and exercise fee to Macrogenics. (See *BioWorld Today*, May 28, 2014.)

From there, the deal structures are similar. The MGD010 agreement involved another $468.5 million in potential clinical, regulatory and commercialization milestones to Macrogenics as well as double-digit royalties on global net sales and the option to co-promote MGD010 with Takeda in the U.S. Macrogenics also secured an option to fund a portion of phase III development in exchange for a North American profit-share.

'COMFORTABLE WITH ALL DIFFERENT TYPES OF STRUCTURES'

The broader agreement underscores Takeda's confidence in Macrogenics' technology and demonstrates that the companies – which had known each other for some time even before inking their first deal in May – are comfortable as collaborators. One goal of the MGD010 partnership was the opportunity for Macrogenics to gain experience from the potential profit-sharing and co-development arrangements with Takeda, with the long-term corporate goal of advancing some internal assets to regulatory approval and commercialization.

Most of the company's early interaction with Takeda came via its Millennium oncology unit, according to Scott Koenig, president and CEO of Macrogenics. When a separate Takeda unit expressed interest in Macrogenics' autoimmune capabilities, "we began speculating on how we could actually build on that initial interest in autoimmune disease and take advantage of the properties of the DART platform mechanistically with combinations of other molecules," he told *BioWorld Today*.

The growing relationship between Macrogenics and Takeda mirrors an existing partnership with Les Laboratoires Servier SA, which also began with a single DART licensing deal for up to $450 million before the Paris-based pharma came back for a broader arrangement encompassing three undisclosed tumor targets, with a potential $1 billion payday. (See *BioWorld Today*, Dec. 1, 2011, and Sept. 20, 2012.)

"We have a very open view on how to create new business partnerships," Koenig said, adding that he encourages the business development team to "think broadly and think strategically. We're very comfortable with all different types of structures."

The company now has six DART-based deals, including two – with Ingelheim, Germany-based Boehringer Ingelheim GmbH (BI) and Pfizer Inc., of New York – that were nailed down in a single day during 2010. Terms of the Pfizer deal, in cancer, were not disclosed, but the BI arrangement could be worth more than $2 billion for exploring therapeutic areas that include immunology, oncology, respiratory, cardiometabolic and infectious diseases. (See *BioWorld Today*, Oct. 27, 2010.)

In June, Macrogenics advanced its first DART molecule, MGD006, into clinical development in acute myeloid leukemia. The company holds development and commercialization rights to MGD006 in most of North America, Japan, South Korea and India, while partner Servier has rights in other countries.

The investigational new drug (IND) application for its second DART molecule, MGD007, also was approved this summer, and Macrogenics expects to advance that compound – also partnered with Servier – into clinical development in the second half of the year.

Almost a year ago, the company closed its initial public offering, raising $80 million, which it followed up with a public offering in February. (See *BioWorld Today*, Oct. 11, 2013, and Feb. 14, 2014.)

As evidenced by its billion-dollar-plus deals, Macrogenics is eager to work with new and existing collaborators – for the second and even the third time, Koenig said – to introduce new technologies and targets for drug development. He predicted the company will file INDs for three more DART-based compounds in 2015.

In the meantime, data from a phase II trial of margetuximab (MGAH22), the company's Fc-optimized monoclonal antibody that targets and binds to the HER2 protein, in HER2-positive breast cancer are expected to report in the first half of 2015. Initial data from dose-expansion cohorts of the company's

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Pfizer

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Pfizer Inc. entered an agreement with Kyowa Hakko Kirin Co. Ltd. to study the effect of a combination of two of their drug assets, Pfizer's PF-05082566 and Kyowa Hakko Kirin's mogamulizumab.

Biotech companies are increasingly looking at immunotherapy drugs to fight cancer. It is still early days for immunotherapies, but they emerged as a key topic during the recent European Society of Medical Oncology meeting in Spain. Multinational companies like Astrazeneca plc, Merck & Co. Inc., Roche Holdings AG and Bristol-Myers Squibb Co. are looking at immunotherapies. (See *Bioworld Today,* May 6, 2014, and Sept. 30, 2014.)

The collaboration by Prizer and Kyowa Hakko Kirin builds on that work.

PF-05082566 is an investigational, fully humanized monoclonal antibody (MAb) that stimulates signaling through 4-1BB (CD-137) proliferation and survival. CD-137 is a protein involved in the regulation of immune cell activation.

Mogamulizumab is an anti-C-C chemokine receptor 4 (CCR4) antibody that suppresses some of the immune cells that shield the tumor from the immune system.

"PF-05082566 and mogamulizumab are anticipated as part of a new class of cancer treatments known as immunotherapies, which use the body's own immune system to help fight cancer," said Kazuaki Inoue, manager of Kyowa Hakko Kirin's public relations department.

Preclinical studies have shown that PF-05082566 enhances T-cell mediated immune responses to fight against tumors. It is currently being evaluated in a phase I study as a single agent in multiple tumor types.

Pfizer is also conducting several combination studies, including one that combines PF-05082566 with Rituxan (rituximab, Biogen Idec Inc. and Roche AG) in non-Hodgkin lymphoma patients.

Rituximab is a chimeric monoclonal antibody against protein CD20 found on the surface of immune system B cells. Rituximab is often used to treat lymphoma, leukemia and autoimmune disorders.

PF-05082566 hasn't been approved for any indications in any countries yet.

Mogamulizumab is designed to kill its target cells through potent antibody-dependent cellular cytotoxicity. The drug was launched in Japan in May 2012 for the treatment of patients with relapsed or refractory CCR4-positive adult T-cell leukemia-lymphoma and, in March of this year, granted expansion approval for the treatment of patients with relapsed or refractory CCR4-positive, peripheral T-cell lymphoma and cutaneous T-cell lymphoma. Mogamulizumab is also being studied in the U.S., European Union and other countries.

Pfizer and Kyowa Hakko Kirin will co-fund the clinical research, but Pfizer has taken up responsibility to conduct the trials. A phase Ib study aims to evaluate the safety and tolerability of the combination in patients with solid tumors. "Pfizer plans to conduct the study in the U.S.," Inoue said.

The study will help establish a recommended dose regimen for the combination and also assess its safety and preliminary efficacy. Pfizer plans to initiate the study in 2015, and the future development will be based on those results.

"We are committed to progress our immuno-oncology pipeline as rapidly as possible, and we believe that combination therapies have the potential to be one of the most effective ways of treating cancer," Inoue said. "Partnerships such as the one we have entered with Pfizer will support our drive to deliver new medicines to patients, re-shaping the way we treat cancer."

For Pfizer, the latest collaboration "provides an additional important partnership opportunity to explore the potential of 4-1BB as part of a novel immunotherapy combination regimen." said Mace Rothenberg, senior vice president of clinical development and medical affairs and chief medical officer for Pfizer Oncology.

Pfizer previously announced an agreement with Merck & Co. Inc. to study the combination of Merck's MK-3475 with two Pfizer oncology assets. MK-3475 is an investigational anti-PD-1 immunotherapy designed to restore the immune system's ability to recognize and target cancer cells. The companies will conduct phase I and phase II studies to evaluate the safety and efficacy of the combination of MK-3475 and Pfizer's tyrosine kinase inhibitor, axitinib, in renal cell carcinoma. Another phase I study will evaluate the safety and tolerability of the combination of MK-3475 and PF-05082566.

"We believe that combination therapy in immuno-oncology holds great promise to improve outcomes for patients with cancer and provides an exciting opportunity for Pfizer to maximize the potential of our emerging immuno-oncology portfolio," Rothenberg said.

Yoichi Sato, managing executive officerand head of the research and development division at Kyowa Hakko Kirin, called the collaboration with Pfizer "an important component of Kyowa Hakko Kirin's ongoing transformation into a global specialty pharmaceutical company."

"With recent progress in the field of cancer immunotherapy, the combination therapy of mogamulizumab and Pfizer's 4-1BB agonist has the potential to bring significant benefits to patients," Sato said.

Founded in 1949, Kyowa Hakko Kirin focuses on developing drugs in the therapeutic areas of oncology, nephrology and immunology. //

Obesity

Continued from page 1

used for weight control, providing a promising target for the development of novel obesity drugs.

The scientists, a collaboration of researchers from the Shanghai Institute of Materia Medica, Shanghai Institute of Organic Chemistry and Tongli University in Shanghai, reported their findings in the Sept. 22, 2014, early online edition of the *Proceedings of the National Academy of Sciences*.

Affecting more than 1.4 billion adults worldwide, according to the World Health Organization (WHO), obesity is a leading cause of illness, being associated with a number of potentially preventable diseases, including cardiovascular disease, type 2 diabetes mellitus, dyslipidemias, osteoarthritis and certain cancers.

Obesity is also a leading cause of global mortality, with roughly 3.4 million adults dying each year as a result of being overweight. In addition, WHO estimates that 44 percent of diabetes, 23 percent of ischemic heart disease and 7 percent to 41 percent of certain cancer cases are attributable to obesity.

While many of those conditions can be managed effectively by weight loss through dietary restriction and regular exercise, many patients find such lifestyle changes difficult to maintain in the long term and look to pharmacological treatments to help with weight control.

Nevertheless, despite the massive market potential for obesity medications, just three such treatments have been approved by the FDA: selective serononin 5-HT2c receptor agonist Belviq (lorcaserin, Arena Pharmaceuticals), Qsymia (phentermine/topiramate, Vivus Inc.) and, most recently, Contrave (naltrexone/bupropion, Orexigen Therapeutics Inc.) (See *BioWorld Today*, Sept. 12, 2014.)

However, those agents have limited efficacy in promoting weight loss and also are associated with significant side effects, prompting the search for alternatives, with herbal-based food supplements proving particularly popular in that regard.

Herbal dietary supplements are the most commonly used alternative obesity treatments, although little is known about their efficacy, safety and mechanisms of action, which might provide clues for development of novel obesity medications.

Among those supplements, the African cactus *Hoodia gordonii* is of particular interest, having been used for thousands of years by southern African aborigines as an effective appetite and thirst suppressant during their extended hunting expeditions. It has therefore been proposed as a new obesity agent. The cactus is rich in steroidal glycosides, but only one such molecule, called P57, has so far been shown to cause appetite loss, although its development has been hindered by intellectual property controversies and the lack of a clear mechanism of action.

More recently, GRP119, a G protein-coupled receptor that is highly expressed in pancreatic B cells and in intestinal L cells, has been shown to facilitate glucose-stimulated insulin and glucagon-like peptide-1 (GLP-1) secretion. As such, GRP119 has been proposed as an attractive new target for the treatment of type 2 diabetes and obesity.

In order to search for new GPR119 agonists, Chinese researchers led by Xin Xie, a professor and principle investigator in the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, deputy director of Chinese National Center for Drug Screening and an adjunct professor in Tongji University, screened a library of approximately 4,400 natural products.

"We screened 4,400 compounds isolated from natural resources, including herbs," Xie told *BioWorld Today*. "We established a cell line expressing GPR119 and a reporter system," she explained. "Once GPR119 was activated by a screened compound, a luciferase reporter system was expressed and we could detect this change."

The researchers identified a steroid glycoside that was isolated from the *H. gordonii* cactus called Gordonoside F, which, unlike P57, was demonstrated to be able to specifically activate GPR119.

The Gordonoside F molecule was then successfully synthesized by a team of organic chemists headed by Xie's collaborator, Biao Yu, a professor, principle investigator and director of the State Key Laboratory of Bio-organic and Natural Products Chemistry at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

Gordonoside F was shown to promote glucose-stimulated insulin secretion, both in vitro and in vivo, and to significantly reduce food intake in mice. Moreover, those effects proved to be mediated by GPR119, because GPR119 gene knockout in mice was shown to prevent the therapeutic effects of the *H. gordonii* extract.

"We have demonstrated for the first time, to our knowledge, that GPR119 is a direct target and one of the major mechanisms underlying the therapeutic effect of the popular 'weight loss' herb *H. gordonii*," Xie said.

In the past "the development of *H. gordonii* and P57, a previously reported active component, has been hindered by intellectual property issues and limited resources," she noted. "Gordonoside F has no such problems and could be developed into drugs for the treatment of metabolic disorders.

"Given the long history of safe application of this herb in weight control, it is foreseeable that the novel molecular scaffold of Gordonoside F will provide a promising opportunity to develop new drugs in treating metabolic diseases," Xie added. "Gordonoside F could serve as a starting point for structural modification. Hopefully, we could identify better GPR119 agonists.

"We are now modifying the structure of Gordonoside F, which is bulky and complicated. We want to identify derivatives of Gordonoside F with a simpler structure, but with better potency in activating GPR119." //

Oncore

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space in a big way.

The most recent, with the ink still wet on the page, was an all-cash acquisition of privately held Enantigen Therapeutics Inc., giving Oncore control of Enantigen's two discovery programs in HBV. One of those targets the inhibition of surface-antigen (s-antigen) secretion while the other targets capsid assembly inhibition.

The companies were neighbors at the Pennsylvania Biotechnology Center in Doylestown, also the home of the Hepatitis B Foundation and the Foundation's research center, the Baruch S. Blumberg Institute, where Oncore originally struck deals for its internal assets. Oncore had "eyes on" Enantigen almost from the time of its own launch, according to Patrick Higgins, Oncore's CEO. That move came within a year after Oncore's founders orchestrated the $11 billion buyout of their previous company, Pharmasset Inc., by Gilead Sciences Inc. (See *BioWorld Today*, Nov. 22, 2011.)

Days before that deal, Pharmasset had launched pivotal phase III studies of its all-oral, interferon-free hepatitis C virus (HCV) nucleotide analogue, then known as PSI-7977. Following the acquisition, the compound became GS-7977, then sofosbuvir, before it was approved last year as the blockbuster Sovaldi. (See *BioWorld Today*, Nov. 2, 2011, and Dec. 10, 2013.)

Higgins, who was Pharmasset's executive vice president of sales and marketing at the time of the Gilead acquisition, took some time to investigate "the state of the science" in HBV, both in academia and biotech, before gathering an all-Pharmasset leadership team at Oncore. The other co-founders are Michael Sofia, chief scientific officer and R&D head, who was head of chemistry and an inventor of Sovaldi; Mike McElhaugh, chief operating officer, who was director of business development and market analytics at Pharmasset; and Bryce Roberts, chief legal officer, who was vice president and senior counsel at Pharmasset – duties he also assumed, for a time, at Gilead.

Oncore's platform technology focuses on inhibiting the formation, controlling transcription and destabilizing HBV covalently closed circular DNA (cccDNA), thought by some to represent the best opportunity to cure chronic HBV-infected patients, according to Higgins. Oncore's strategy is to target cccDNA with the goal of achieving a "functional cure" by combining agents against cccDNA with other direct-acting antiviral mechanisms and strategies to boost the patient's immune response.

Enantigen's approach targets HBV s-antigen (HBsAg), a key viral protein involved in controlling the host immune response. HBsAg exists in large quantities not only as a constituent of HBV virions but also in HBV subviral particles, which significantly outnumber infectious virions circulating in the body. HBsAg has been shown to inhibit the innate immune response through effects on T-cell and dendritic cell function, so the inhibition of HBsAg production or secretion could reduce the impact of the viral infection on the host's immune function.

"Our goal is to bring multiple technology assets into the program that actually will hit various targets on the viral cycle," Higgins explained. "The additional target that Enantigen provides is the s-antigen inhibition."

The Enantigen buy also gives Oncore a second capsid assembly inhibitor program – another lynchpin in its multipronged HBV drug development effort. Oncore's internal cccDNA program targets the eradication of viral genomic material characteristic of HBV, according to Sofia. Covalently closed circular DNA transcription produces HBV pregenomic RNA, or pgRNA, which is bound covalently to the HBV viral polymerase. The entire complex must be encapsidated by a sphere of viral capsid proteins to continue the viral lifecycle. By inhibiting pgRNA encapsidation, Oncore hopes to halt that progression and prevent viral replication.

"We realized early on in our strategic planning that hepatitis B – like other viruses, such as HIV and HCV – requires a combination therapy approach, using drugs with different mechanisms of action," Sofia explained. "We set out very early to understand what mechanisms were being studied and focus on trying to acquire assets across a wide variety of therapeutic areas in the field. We're trying to cover our bases, as best as possible, with assets that target key steps in the virus replication cycle as well as the immune modulatory strategy."

Members of Enantigen's team, headed by Michael Xu, president and chief operating officer, are expected to join Oncore to help accelerate the development of its HBV pipeline. Xu and Sofia, both chemists, had known each other for some time before the deal.

'A BROADER BASE OF THE VIRAL TARGET THAN ANYBODY ELSE'

Oncore started September by closing a series R, or roll-up, financing, using the same strategy pursued during an early round at Pharmasset. Higgins declined to name the single investor or disclose the amount but said the funding allowed the company to consolidate a number of drug candidates into a single HBV platform company. "We're experts at this," he told *BioWorld Today*.

A few days later, the company inked an exclusive global license with Neurovive Pharmaceutical AB, of Lund, Sweden, encompassing a series of second-generation cyclophilin inhibitors to treat HBV. The potential $150 million deal included an undisclosed up-front payment, development and sales milestones, and royalties on product sales.

The deal with Neurovive, which specializes in mitochondrial drugs, gave Oncore access to cyclophilin inhibitors known as sangamides, based on Neurovive's polyketide chemistry platform. Data presented in April at the International Liver Congress suggested that Neurovive's lead cyclophilin compound, NVP108, appeared to inhibit HBV by two mechanisms in vitro, directly inhibiting several stages of viral replication in liver cells and indirectly strengthening the host immune response via

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Cortellis

Continued from page 1

drugs mentioned in lead articles. If you need to take a deeper dive into a company, to assess the development of a drug candidate or to check out the competitive landscape, just click through and take Cortellis for a test drive. For more information about Cortellis, call +1-800-336-4474 in North America or, outside of the U.S. and Canada, +44-203-684-1796.

Macrogenics

Continued from page 4

immuno-oncology drug, MGA271, in solid tumors are expected next year, as well.

In a flash note, Leerink Partners LLC analyst Michael Schmidt declared the new Takeda platform deal "confirms MGNX leadership in [the] bispecific MAb space." Reiterating the company's "outperform" rating, he called the deal terms "extremely favorable" for Macrogenics, reflecting "management's ability to capitalize on its platform asset and generate value for shareholders."

On Tuesday, the company's shares (NASDAQ:MGNX) gained 89 cents to close at $20.90. //

FINANCINGS

Tesaro Inc., of Waltham, Mass., closed its underwritten public offering of $201.25 million in 3 percent convertible senior notes due 2021, including $26.25 million in notes issued to exercise in full the underwriters' option to fill overallotments. The notes, which mature on Oct. 1, 2021, may be converted into cash, Tesaro common shares or a combination of cash and shares, at the company's election. The company said most of the net proceeds of approximately $194.71 million will be used to fund commercialization activities for rolapitant (oral formulation) and clinical trials for rolapitant (intravenous formulation), niraparib and Tesaro's other product candidates; to execute Tesaro's immuno-oncology platform strategy; and for other corporate purposes. Citigroup and Deutsche Bank Securities acted as joint book-running managers for the offering, with Leerink Partners, Baird and BMO Capital Markets as co-managers.

OTHER NEWS TO NOTE

Cellular Biomedicine Group Inc., of Palo Alto, Calif. completed its acquisition of privately-held **Agreen Biotech Co. Ltd.**, of Beijing, and its founder's U.S. patent for about $3.3 million in cash and the issuance of 822,522 shares of common stock, subject to a one-year lock-up period from the date of the agreement. Cellular said the move would accelerate its strategy to grow its cancer immune cell therapy segment with a platform that presents the potential to complement or replace invasive chemotherapy for certain cancers. (See *BioWorld Today*, Aug. 13, 2014.)

Evotec AG, of Hamburg, Germany, said its multitarget collaboration with Bayer Healthcare, a subsidiary of Leverkusen, Germany-based **Bayer AG**, has reached an important milestone for the transition of a molecule into preclinical development for the treatment of endometriosis. That milestone was achieved under the agreement between Evotec and Bayer signed in October 2012. The goal of the collaboration is to develop three clinical candidates within the five-year alliance.

Sunshine

Continued from page 1

and devicemakers to doctors and medical schools.

Despite ongoing criticism from doctors and industry that the database may create confusion by failing to provide appropriate context for some payments, CMS, legislators and consumer advocates argue it will create greater transparency around the flow of money in the U.S. health care system, an area that's famously opaque.

Both parties won partial victories Tuesday, as CMS withheld personally identifiable information tied to about 40 percent of the records in the database while it works with reporting entities to tackle corrections and disputes. Further hampering access to detail submitted to CMS, the project's website slowed to a crawl Tuesday afternoon, leaving searches hanging.

The Sunshine Act-mandated database includes payments made to doctors for their roles as clinical investigators, researchers and consultants, including fees paid for representing companies at FDA advisory committee meetings and in other capacities. But it also includes payments that some doctors worry may cast doubt on the impartiality, such as travel reimbursements and other gifts companies provided to physicians and teaching hospitals during the last five months of 2013. Altogether, it contains 4.4 million payments valued at nearly $3.5 billion attributable to 546,000 individual physicians and almost 1,360 teaching hospitals.

"Consumers have more information about the products they use than ever before, but health care is still behind the curve," wrote Charles Grassley, R-Iowa, and a co-author of the Physician Payment Sunshine Act, in an op-ed published in *The Des Moines Register* ahead of the database release. "A lot of smart people believe health care costs would go down and quality would improve if we pulled back the curtain on where the money goes,"

DOCTORS WORRY FOR THEIR REPUTATIONS

Data included in the CMS database is, in some ways, akin to credit card transactions. It reflects financial exchanges without illuminating much about why the transaction took place and sometimes contains inaccuracies. Furthermore, in the aggregate, the data could color perceptions of how trustworthy doctors and included medical institutions are, creating a risk of "conveying a distorted image of certain physician-industry relationships," suggested doctors who wrote a letter published Tuesday in the *Annals of Internal Medicine*.

"The public deserves accurate, accessible information about third-party payments to physicians that may affect their care," the doctors, including Johns Hopkins bioethicist Stephanie Morain, wrote. "Yet, disclosures must be presented in a manner not prone to misinterpretation. Misinterpretation, or fear of it, could undermine physician participation in important health research."

While the 200,000 doctors covered by the regulation were initially given a 45-day window to dispute records tied to their names, the American Medical Association said that window was too short and did not provide timely notice, even when the deadline was extended because of service interruptions on the Open Payments website that hobbled doctors' ability to review and seek correction of the data.

Just a fraction of the entities covered – more than 26,000 physicians and 400 teaching hospitals – registered in the Open Payments system to review payments attributed to them, CMS said. In cases where CMS was unable to match the physician information or the record was not available for review and dispute but the company had attested that the payment had been made, the personally identifiable information has been suppressed temporarily in the record, CMS said. The agency plans to make the data fully identifiable sometime next year after providing a further opportunity for those covered to review and correct records, though it did not specify a timeline for that process.

VIEWS FOR THE PUBLIC AND DATA GEEKS

Data released Tuesday included web-viewable breakouts and special hooks for computer programmers to access and make use of data on general, nonresearch and non-ownership-related payments made to physicians and teaching hospitals, research-related payments and ownership and investment payments.

In addition to the recipients of payments chronicled in the new Open Payments database, drugmakers and others spending money to advance medical care and sales figures face a growing and often unpredictable raft of state and federal disclosure rules. (See *BioWorld Today*, April 22, 2014.)

The Pharmaceutical Research and Manufacturers of America (PhRMA) voiced general support for the Sunshine Act's implementation, suggesting in PhRMA's words that it will "play an important role in advancing innovation and science," but was worried about the final presentation of the data. In the end, CMS described the context included in the database to PhRMA at a very high level, but did not provide the organization an opportunity to review it directly. John Murphy, associate general counsel, said PhRMA hopes to work with CMS to refine the data collection process and content structure for the next iteration of the database.

Biotechnology Industry Organization (BIO) President and CEO Jim Greenwood said that it's "disappointing that CMS failed to provide the necessary context about these disclosures – and how they should be read." BIO is concerned that some third parties will attempt to misuse the data, "potentially threatening innovation in our nation's health care system." Greenwood added that BIO will work with CMS and others to ensure an appropriate context is quickly provided.

AN INCREMENTAL APPROACH

While the launch of the Open Payments database itself is new, at least 17 drugmakers have already publicly reported financial

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Yakult

Continued from page 1

of a phase I trial and the launch of phase II development.

Frankfurt–based 4SC AG, a discovery and development company that targets small-molecule drugs for cancer and autoimmune diseases, said its Japanese partner, Yakult Honsha Co. Ltd., successfully completed a phase I study for 4SC's epigenetic cancer compound resminostat (4SC-201) in combination with cancer drug Nexavar (sorafenib, Amgen Inc. and Bayer AG). Yakult has now launched a multicenter, randomized phase II study.

Yakult Honsha is best known for a fermented milk drink that is popular across Asia, but it also has pharmaceutical and cosmetic businesses. The company is a market leader in gastrointestinal cancer therapeutics in Japan.

Under the terms of their 2011 collaboration, 4SC granted an exclusive license to Yakult for the development and commercialization of resminostat in Japan. Yakult will be responsible for all clinical requirements for the development of the drug in oncology indications.

Resminostat is an oral histone deacetylase (HDAC) inhibitor with an innovative epigenetic mechanism of action that could enable the compound to be deployed as a targeted tumor therapy for a broad spectrum of oncological indications, in particular in combination with other cancer drugs.

Resminostat has been investigated in HCC, Hodgkin's lymphoma (HL), colorectal cancer (CRC) and non-small-cell lung cancer (NSCLC) and has demonstrated antitumor activity in a phase II SAPHIRE trial in patients with advanced HL. The overall response rate was 34 percent, and the drug showed clinical benefits in 54 percent of patients who were heavily pre-treated. The drug also demonstrated good safety and tolerability.

The resminostat/sorafenib combination already has shown a clean safety profile in European HCC patients.

4SC said Yakult completed the phase I safety study with resminostat in Japanese patients with advanced solid tumors in May and is now investigating the drug in HCC and NSCLC.

Yakult's dose-escalation phase I study in nine advanced HCC patients of Asian origin confirmed that the resminostat/sorafenib combination is safe and well tolerated. Should the drug make it through the development process it would create another option for HCC patients in Japan that currently have few alternatives, even though the incidence of HCC is high.

The success of the trials in Japan is another positive indication for 4SC's planned clinical development program for resminostat in Western countries.

The development of resminostat in the Japanese market is "of high strategic importance to 4SC given the high incidence of HCC in the region," Jochen Orlowski, 4SC's head of corporate communications and investor relations, told *BioWorld Today*.

"From 4SC's perspective, this is significant progress because the resminostat/sorafenib combination has been shown to be safe and well tolerated in Asian (i.e. Japanese and Korean) HCC patients," Orlowski said. "The clean safety of the resminostat/sorafenib combination is a key prerequisite for the further phase II development of the combination in Asian HCC patients."

Based on the result of the phase I study, Yakult's phase II trial will compare the efficacy of the resminostat/sorafenib combination vs. sorafenib alone as a first-line treatment in up to 140 patients with advanced HCC. All patients enrolled have to be previously untreated with systemic chemotherapy.

The primary endpoint will be time to progression (TTP). Secondary endpoints are overall survival (OS), progression-free survival (PFS) and safety. The study also will evaluate the ZFP64 biomarker, as the set of patients with high levels of ZFP64 gene expression at baseline showed a statistically significant increase of median overall survival compared with patients with low ZFP64 expression levels.

Enno Spillner, CEO of 4SC, described the company's Japanese partner as one with "great enthusiasm and energy" in the development of reminostat.

"In parallel, we will continue to drive forward the preparation of our own clinical development plans with resminostat in first-line HCC in the Western world," Spillner said.

4SC has completed open-label trials in Europe in three indications: HCC (phase IIa, in combination with sorafenib), HL (phase IIa in monotherapy) and colorectal cancer (phase I in combination with FOLFIRI).

4SC is currently preparing a phase IIb study in Western patient populations, which is planned to investigate the resminostat/sorafenib combination vs. sorafenib plus placebo in first-line advanced HCC. That trial could commence in early 2015 and is dependent on financing.

Yakult paid €6 million (US$7.64 million) up front for the Japanese rights to reminostat and will pay up to €127 million upon achieving specific clinical and regulatory milestones in Japan. In addition to that, Yakult Honsha also will pay 4SC double-digit royalties linked to product sales.

Yakult has also worked with other partners on several of its drugs. It worked with Proacta Inc. in the development of hypoxia-activated prodrug PR610, and it has been involved in the development of the P13k/Akt inhibitor perifosine with Aeterna Zentaris Inc. It also has worked with Livtech Inc. in the humanized monoclonal anticancer antibodies program, LIV-2008, and is involved in the development of antibody biosimilars with UMN Pharma Inc. and API Co.

Yakult's pharmaceutical revenues dropped in the last fiscal year, ending March 31, 2014, due to lower sales of its core product Elplat, a drug used to treat colorectal cancer. The company said it plans to strengthen its efforts in the field of oncology by expanding the number of indications for Elplat to gastric cancer. //

Oncore

Continued from page 7

interferon regulatory factors, or IRFs, including inhibition of an interaction between cyclophilin A and IRF9, a key component of the Jak/Stat pathway. Data also suggested that the risk of developing resistance to NVP018, a significant issue in hepatitis treatment, was low. Preclinical studies on NVP018 are nearly complete, and Oncore expects to move the compound into human trials next year, according to Higgins.

Oncore – the name alludes to the "encore" effort by the "core" team at Pharmasset – isn't seeking a head-on confrontation with erstwhile suitor Gilead. But even though the company isn't pursuing HCV, where Gilead has planted a very big global stake, the quest for an HBV cure likely will land Oncore right back where it started. Gilead is advancing tenofovir alafenamide (nucleotide reverse transcriptase inhibitor), or TAF, as well as GS-4774 (tarmogen T-cell immunity stimulator) and GS-9620 (TLR-7 agonist) in chronic HBV.

TAF also is part of the company's once-daily single tablet regimen of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg in HIV. Just last week, Gilead reported data from two phase III trials (Studies 104 and 111) showing the TAF regimen met the primary endpoints in treating HIV-1 infection in treatment-naïve adults, demonstrating noninferiority to Stribild (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) with more favorable renal and bone safety. Based on the findings and data from ongoing phase III studies of the combo drug, Gilead said it will submit regulatory applications for the regimen in the U.S. and European Union this year.

As a single agent, TAF is in phase III development in HBV, with Gilead's other candidates in phase II. That puts Gilead's HBV development timetable far ahead of Oncore's.

Based on the speed in which Oncore was assembled and other moving parts were locked into place – not to mention the team's experience in the hepatitis space – Higgins is unconcerned. Though the Enantigen buy is probably not the last strategic move by Oncore, it puts the company in a position to cover "a broader base of the viral target than anybody else that's out there," he maintained.

Oncore's team already is looking to replicate its success at Pharmasset through aggressive internal development and global licensing deals that allow it to pursue related indications, such as liver fibrosis and hepatocellular carcinoma. Higgins expects little trouble attracting attention from the investment community along the way, hinting that a run at the public markets might not be far away.

"There are investors who were with us at Pharmasset, and most of those investors have a mandate to be in the public market," he said. "I think we'll have to consider that down the road." //

OTHER NEWS TO NOTE

Glialogix Inc., of San Francisco, said it entered a sponsored research agreement with Fast Forward, a nonprofit organization established by the National Multiple Sclerosis Society, which will provide funding to the company for preclinical studies of GLX1112, a neuroprotective therapy designed to slow the accumulation of disability in progressive multiple sclerosis. The research to be funded will include advanced pharmacokinetic testing, preclinical models and further mechanistic studies of GLX1112.

Mymetics Corp., of Epalinges, Switzerland, said its HV vaccine candidate will enter a new preclinical trial to confirm results obtained in a previous trial. The research, which will be funded by the Bill & Melinda Gates Foundation, will involve 36 rhesus monkeys and will compare two antigen vaccination regimens to placebo, followed by intravaginal challenges with live virus that carries an envelope that differs from the one in the vaccine preparation. Results are expected at the end of 2015. Mymetics' vaccine candidate is produced through its virosome technology and antigen design.

Sunshine

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relationships with doctor and others through agreements reached through settlements with the U.S. Department of Justice. Those data, going back to 2009, has been compiled by the nonprofit investigative journalism organization, Propublica in cooperation with Pharmashine, a project of Obsidian Healthcare Disclosure Services LLC, leading to the publication of numerous analyses already that have shaped industry practicies.

While CMS plans to publish future payment reports annually with full-year payment data, beginning in June 2015, it was unclear from the agency's statement Tuesday whether it planned to backfill using company data from earlier years to achieve a similar resource. It will not, apparently, pass judgement on patterns observed at first.

"Open Payments does not identify which financial relationships are beneficial and which could cause conflicts of interest," said Shantanu Agrawal, deputy administrator and director of the Center for Program Integrity at CMS. "It simply makes the data available to the public. So while these data could discourage payments and others transfers of value that might have an inappropriate influence on research, education and clinical decisionmaking, they could also help identify relationships that lead to the development of beneficial new technologies." //

IN THE CLINIC

Acasti Pharma Inc., of Laval, Quebec, reported top-line data for its pharmacokinetic trial testing the bioavailability and safety of Capre on healthy individuals taking single and multiple daily oral doses of its investigational candidate composed of highly concentrated omega-3 phospholipid for the prevention and treatment of certain cardiometabolic disorders. The open-label study enrolling 42 subjects showed that Capre pharmacokinetics appear to be approximately dose proportional over the 1 g to 4 g per day dose range. Following a single daily dose, Capre reached steady state (EPA and DHA levels plateaued) within seven days of dosing. The compound was safe and well tolerated.

Cytrx Corp., of Los Angeles, said it started a phase IIb trial testing aldoxorubicin, the company's modified version of doxorubicin, vs. topotecan in subjects with extensive-stage small-cell lung cancer (SCLC) who have relapsed or were refractory to prior chemotherapy. The open-label study is expected to enroll about 132 patients and will measure progression-free survival (PFS) as the primary endpoint. Secondary endpoints will include overall survival, overall response rates and safety. Enrollment is expected to be completed in 2015 and PFS data are anticipated by mid-2016. Cytrx previously received orphan drug designation for aldoxorubicin in SCLC.

Dandrit Biotech A/S, of Copenhagen, the subsidiary of Dandrit Biotech USA Inc., signed a contract of collaboration with the University Hospital IRCCS "San Martino" National Institute for Cancer Research known as the San Martino Hospital of Genoa. The collaboration relates to a phase III adjuvant study of Dandrit's cancer vaccine in stage IV colorectal cancer (CRC) patients with no evidence of disease. The primary goal is to evaluate the efficacy of Melcancervac in CRC patient rendered disease-free after the completion of standard treatments in accordance with local practices.

Erytech SA, of Lyon, France, reported phase III results from its pivotal study of Graspa (L-asparaginase) in acute lymphoblastic leukemia (ALL), with one-year follow-up showing that the trial met both of its primary endpoints, defined as showing superior safety, expressed as a significant reduction of the incidence of allergic reactions with Graspa compared to the control group, and showing noninferior duration of asparaginase activity above the threshold of 100 IU/l during the induction phase in the non-allergic patients. Results showed that none of the 26 patients in the Graspa arm experienced an allergic reaction vs. 12 of the 28 (42.9 percent) patients treated with reference L-asparaginase in the control group (p < 001). And, in the Grapsa group, asparaginase levels were maintained above 100 IU/l for an average of 20.5 days with up to two injections during the first month of treatment (induction phase) vs. 9.2 days in the control group with up to eight injections of reference L-asparaginase (p<001). Secondary efficacy endpoints analyzed so far confirm the favorable clinical efficacy profile of Graspa, and the study also shows favorable results in patients with prior allergies to L-asparaginase. The study, GRASPIVOTALL, was a phase II/III study involving 80 children and adults with relapsing or refractory ALL.

OTHER NEWS TO NOTE

Novamedica LLC, of Moscow, and **Horus Pharma SL**, of Saint-Laurent-Du-Var, France, signed a partnership agreement that grants Novamedica exclusive rights to commercialize a portfolio of products in Russia and the Commonwealth of Independent States. Products include: hyaluronic acid containing ILast to assist healing of the eyelids following surgery; easy to swallow Macula-Z-Oro combining essential vitamins for eye health antiseptic; and single dose and preservative-free vitamin B12 eye drops to promote healing. The first sales from that portfolio of products are expected in 2015, and Novamedica will have the option to commercialize future Horus products currently under development, with special focus on glaucoma treatment.

Oncomed Pharmaceuticals Inc., of Redwood City, Calif. reported that the first small-molecule Wnt pathway inhibitor under its collaboration with Leverkusen, Germany-based **Bayer Pharma AG** is advancing to preclinical development, triggering a $2 million milestone payment to Oncomed. The partners initiated joint discovery efforts to identify small-molecule inhibitors of the key cancer stem cell pathway as part of a collaboration that began in 2010. While they're also advancing two biologics targeting the Wnt pathway, this is the first small-molecule inhibitor under the collaboration to enter preclinical development. (See *BioWorld Today*, June 16, 2014.)

Regenxbio Inc., of Washington, said gene transfer mediated by its NAV AAV8 vectors resulted in sustained serum alpha-L-iduronidase (IDUA) expression, as well as correction of systemic features of MPS I, or Hurler syndrome, a lysosomal storage disease caused by the body's inability to produce the IDUA enzyme. Data from a study performed by researchers at the Perelman School of Medicine at the University of Pennsylvania show animals treated with a single intravenous injection of NAV AAV8 vectors expressing the IDUA gene not only demonstrated meaningful improvements in the biochemical features of MPS I in most tissues, but the majority also exhibited complete resolution of aortic valve lesions. That effect is significant since it has not been previously observed in MPS I patients treated with current therapies or animal models. The study has been published online in the *Proceedings of the National Academy of Sciences*.

Salix Pharmaceuticals Ltd., of Raleigh, N.C., and **Progenics Pharmaceuticals Inc.**, of of Tarrytown, N.Y., gained FDA approval to market expanded use of Relistor (methylnaltrexone) for treatment of opioid-induced constipation (OIC) in patients taking opioids for chronic noncancer pain. The regulatory win unlocks the partners' access to nearly 11 million patients on opioid therapy who experience OIC and for whom traditional laxative treatments are often ineffective, they estimated. The expanded approval was based on results of a randomized, double-blind, placebo-controlled phase III trial in 312 patients. A significantly greater portion of patients taking Relistor 12 mg daily reported having three or more spontaneous bowel movements per week during the four-week double-blind period compared to placebo (59 percent vs. 38 percent). (See *BioWorld Today*, July 15, 2014.)

Tianhe Stem Cell Biotechnologies Inc., an Illinois corporation, and Cord:Use Cord Blood Bank entered an equity and exclusive services agreement in which Tianhe has licensed a series of patented technologies for the isolation of human cord blood-derived multipotent stem cells for possible clinical applications. Tianhe is performing phase I/II trials in China and Spain using its Stem Cell Educator Therapy to treat diabetes and other autoimmune diseases. Terms were not disclosed.

To-BBB BV, of Leiden, the Netherlands, changed its name to BBB Therapeutics BV. The company also said Ferdinand Massari and Pericles Calias have joined BBB as chief medical officer and as chief scientific officer, respectively. Completing the management team are recently appointed CEO Anders Harfstrand, as well as chief financial officer Leon Kruimer and chief business officer Carlos de Sousa, both of whom joined the company in January.

Viralytics Ltd., of Sydney, reported in a poster presentation at the European Society for Medical Oncology congress in Madrid, that preclinical studies have generated further evidence of improved Cavatak anticancer activity when used in combination with immune checkpoint inhibitors. The product is a formulation of a common cold virus that has been shown to preferentially infect and attack cancer cells. The study assessed the activity of Cavatak given in combination with either the mouse homolog of the CTLA-4 monoclonal antibody Yervoy (ipilimumab, Bristol-Myers Squibb), or an anti-PD-1 monoclonal antibody. In both cases, the combination of the checkpoint inhibitor produced superior efficacy outcomes in a two-phased mouse melanoma study, compared to the efficacy of either agent alone.

Zealand Pharma A/S, of Copenhagen, disclosed a time-based milestone payment of €2 million (US$2.5 million) from partner **Helsinn Group**, of Lugano, Switzerland, relating to a license agreement between the two firms on elsiglutide, in development to prevent chemotherapy-induced diarrhea in cancer patients. Helsinn is in final preparations to move the GLP-2 peptide receptor agonist into a phase IIb dose-finding trial, expected to start dosing at the end of this year. (See *BioWorld Today*, Dec. 2, 2008.)

IN THE CLINIC

Merrimack Pharmaceuticals Inc., of Cambridge, Mass., reported additional clinical and biomarker data from a phase II study in ER/PR-positive, HER2-negative metastatic breast cancer, showing that patients with high heregulin mRNA levels achieved a statistically significant benefit from combining the agent MM-121 with exemestane. Updated data from that biomarker subgroup, representing 45 percent of patients with metastatic breast cancer, showed a hazard ratio of 0.26 with a "p" value of 0.003. Data were presented at the European Society of Medical Oncology meeting in Madrid. MM-121 is a fully human monoclonal antibody that targets ErbB3, a cell surface receptor that is activated by the ligand heregulin.

Regeneron Pharmaceuticals Inc., of Tarrytown, N.Y., and **Sanofi SA**, of Paris, said a phase IIa proof-of-concept study of dupilumab, a drug designed to block IL-4 and IL-13 signaling, met all primary and secondary endpoints in patients with moderate to severe chronic sinusitis with nasal polyps who did not respond to intranasal corticosteroids. Dupilumab resulted in a statistically significant improvement in the size of nasal polyps, as measured by endoscopic Nasal Polyp Score, the primary endpoint of the study. Statistically significant improvements in all secondary efficacy endpoints were also observed, including objective measures of sinusitis by CT scan, nasal air flow and patient-reported symptoms (sense of smell, congestion, postnasal drip, runny nose and sleep disturbance). In a pre-specified exploratory analysis, dupilumab-treated patients who also had asthma demonstrated significant improvements in asthma control. The safety profile was consistent with previous studies. The study enrolled 60 patients.

Sarepta Therapeutics Inc., of Cambridge, Mass., reported favorable safety results from the single-ascending-dose portion of a phase I study of AVI-7100, its lead candidate for influenza virus, in healthy volunteers. Data from 40 subjects enrolled in five cohorts showed the drug to be well tolerated, with no reported serious or clinically significant adverse events. A multiple-dose portion will proceed as planned. The trial is being conducted through a collaboration with the National Institute of Allergy and Infectious Diseases. AVI-7100 uses Sarepta's Pmoplus chemistry, which is also the basis for the firm's clinical-stage Ebola and Marburg drug candidates.

Therapeuticsmd Inc., of Boca Raton, Fla., said it opened its Rejoice phase III trial of TX-004HR (Vagicap) to evaluate multiple doses of an applicator-free estradiol for treatment of painful intercourse, a symptom of vulvar and vaginal atrophy, due to menopause. The 12-week, randomized, double-blind, placebo-controlled study will enroll 700 patients and evaluate three doses of TX-004HR in dosing levels of 25 mcg, 10 mcg and 4 mcg, a potentially new low-dose option.

PHARMA: OTHER NEWS TO NOTE

Baxter International Inc., of Deerfield, Ill., said it plans to form a new global innovation and R&D center in Cambridge, Mass., for Baxter's biopharmaceuticals business, which is expected to become a separate, independent global company known as Baxalta Inc. in mid-2015. The company expects to bring together about 400 R&D employees at the innovation center, as well as its business development, oncology and biosimilars teams. The R&D positions that will relocate to the new center are currently based in California and Europe. The new biopharma company will maintain certain R&D operations at its location in Vienna, and will have its corporate headquarters in northern Illinois.

Otsuka Pharmaceutical Development & Commercialization Inc., of Princeton, a unit of Otsuka Pharmaceutical Co. Ltd., and **H. Lundbeck A/S**, of Copenhagen, said the FDA approved a new formulation of Abilify Maintena (aripiprazole) for extended-release injectable suspension – a pre-filled dual-chamber syringe. Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia.

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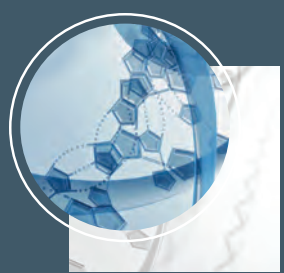

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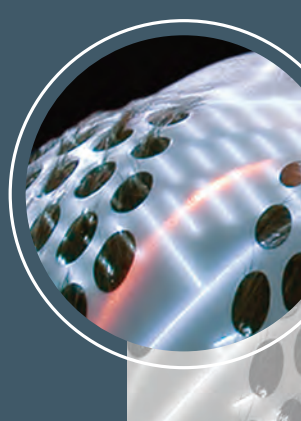

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